XXVI.—*The Alkaloids of Ipecacuanha. Part III.*

By FRANK LEE PYMAN.

IN the previous paper of this series (T., 1917, **111**, 424), it was shown that *O*-methylpsychotrine gave a mixture containing emetine and *iso*emetine* on reduction. The formation of *iso*emetine was demonstrated by the isolation of its benzoyl derivative, for neither *iso*emetine nor any of its salts had at that time been obtained in a crystalline form. Later, however, the *hydrobromide* became crystalline, and was readily purified by crystallisation from water, and, from the pure salt, the *base*, *hydrochloride*, and *hydrogen oxalate* were prepared in the usual manner, and also obtained in crystalline form. On benzoylation, the base gave the benzoyl*iso*emetine previously described. Since emetine and *iso*emetine are produced by the reduction of methylpsychotrine, it was to be expected that *iso*emetine, like emetine, could be oxidised to methylpsychotrine and rubremetine, and this proved to be the case. The view that emetine and *iso*emetine are stereoisomerides was thus confirmed, and it appeared to be of interest to determine whether an equilibrium between the two bases could be established by boiling with amyl alcohol and sodium amyloxide. Experiments to this end were unsuccessful, for, after fourteen hours' boiling, no evidence of partial racemisation was obtained, each base being recovered unchanged except in so far as it had been hydrolysed to phenolic bases.

The fact that psychotrine gives cephaeline and *iso*cephaeline on reduction, whilst the methyl ether of psychotrine gives emetine and *iso*emetine, indicated the probability that *iso*emetine was the methyl ether of *iso*cephaeline, and this has now been proved by preparing *iso*emetine by the methylation of *iso*cephaeline.

When methylated under suitable conditions, *iso*emetine gives a well-crystallised *N*-methyl derivative, N-*methyl*iso*emetine*, which proves to be the *O*-methyl ether of the isomeride of *N*-methylcephaeline previously described (T., 1914, **105**, 1624); this substance is therefore N-*methyl*iso*cephaeline*.

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* The term *iso*emetine is clearly appropriate to this compound, which is the methyl ether of the *iso*cephaeline described in 1914 (Carr and Pyman, T., 1914, **105**, 1591), and the parent of the substance already named benzoyl-*iso*emetine (Pyman, T., 1917, **111**, 424). It has since been employed by Karrer (*Ber.*, 1917, **50**, 582) for a reduction product of rubremetine. Whilst the coincidence is unfortunate, it does not appear to be important, for Karrer's '*iso*emetine'—an amorphous base from which no crystalline derivatives were prepared—is probably a mixture of stereoisomerides.

Complete methylation of *iso*emetine yields a well-crystallised N-*methyl*iso*emetine methiodide*, which is accompanied by an amorphous salt. This is probably a mixture of the two stereoisomeric methiodides of *N*-methyl*iso*emetine, the isomerism of which depends on the presence of an asymmetric nitrogen atom, for it is shown later that the complete methylation of emetine leads to a similar result. This view is borne out by the fact that the crystalline and amorphous salts give N-*methyl*iso*emetinemethine* in equally good yield when converted into the corresponding methohydroxides and evaporated in a vacuum. This methine, like that of emetine, crystallises well as the neutral *oxalate*, and also forms a well-crystallised *methiodide.* So far, attempts to effect its further degradation have not led to crystalline products.

The connexion between the compounds described above and their relation to the compounds described in the previous papers is shown in the diagram on p. 225.

Reference has been made above to the formation of two stereoisomeric methiodides by the complete methylation of emetine. This operation, which consists in heating emetine with methyl iodide and aqueous sodium carbonate, has been carried out previously by several authors, but hitherto only one methiodide has been isolated, although the formation of "by-products" has been observed. In view of the fact that emetine contains a tertiary nitrogen atom common to two ring complexes, the formation of two stereoisomeric *N*-methylemetine methiodides owing their separate existence to the asymmetry of this nitrogen atom appeared to be possible. On experiment, it was found that the product of the reaction gave, besides the previously known methiodide, which melts at 225—226° (corr.) and has $[\alpha]_D - 10°$, a stereoisomeride, which melts at 262° (corr.) and has $[\alpha]_D + 68°$. Proof that this is, in fact, a stereoisomeric *N*-methylemetine methiodide, and not a derivative of some impurity in the emetine employed, is afforded by the fact that it yields the same methine as does the previously known methiodide. In accordance with the usual practice (compare Scholtz, *Ber.*, 1905, **38**, 595; Voss and Gadamer, *Arch. Pharm.*, 1910, **248**, 43; Jowett and Pyman, T., 1913, **103**, 290), the salt of lower melting point is termed the α-salt, that of higher melting point the β-salt. In previous cases, it has been possible to convert the α-salt into the β-salt by heating it above its melting point. α-*N*-Methylemetine methiodide, however, effervesces at its melting point and probably undergoes decomposition, for none of the β-salt could be isolated from the reaction product.

The remarkable influence of stereochemical structure on physiological action, which has been observed in many other cases, is apparent in the case of emetine and *iso*emetine, which differ only in the sign of one asymmetric carbon atom.

Dr. H. H. Dale, F.R.S., of the staff of the Medical Research Committee, has kindly determined the relative toxicity of these compounds, and finds that *iso*emetine is rather less than half as toxic as emetine. The results of intravenous administration of different doses of their hydrochlorides to rabbits were as follows:

Emetine hydrochloride.		iso*Emetine hydrochloride.*	
4·25 mgm.* per kilo.	—All died.	9·0 mgm.* per kilo.	—All died.
4·0 ,, ,,	—4 died out of 5.	8·5 ,, ,,	—4 died out of 6.
3·75 ,, ,,	—1 died out of 4.	8·25 ,, ,,	—3 died out of 6.
3·5 or less ,,	—All lived.	8·0 ,, ,,	—1 died out of 4.
		7·5 or less ,,	—All lived.

* Of the anhydrous salt.

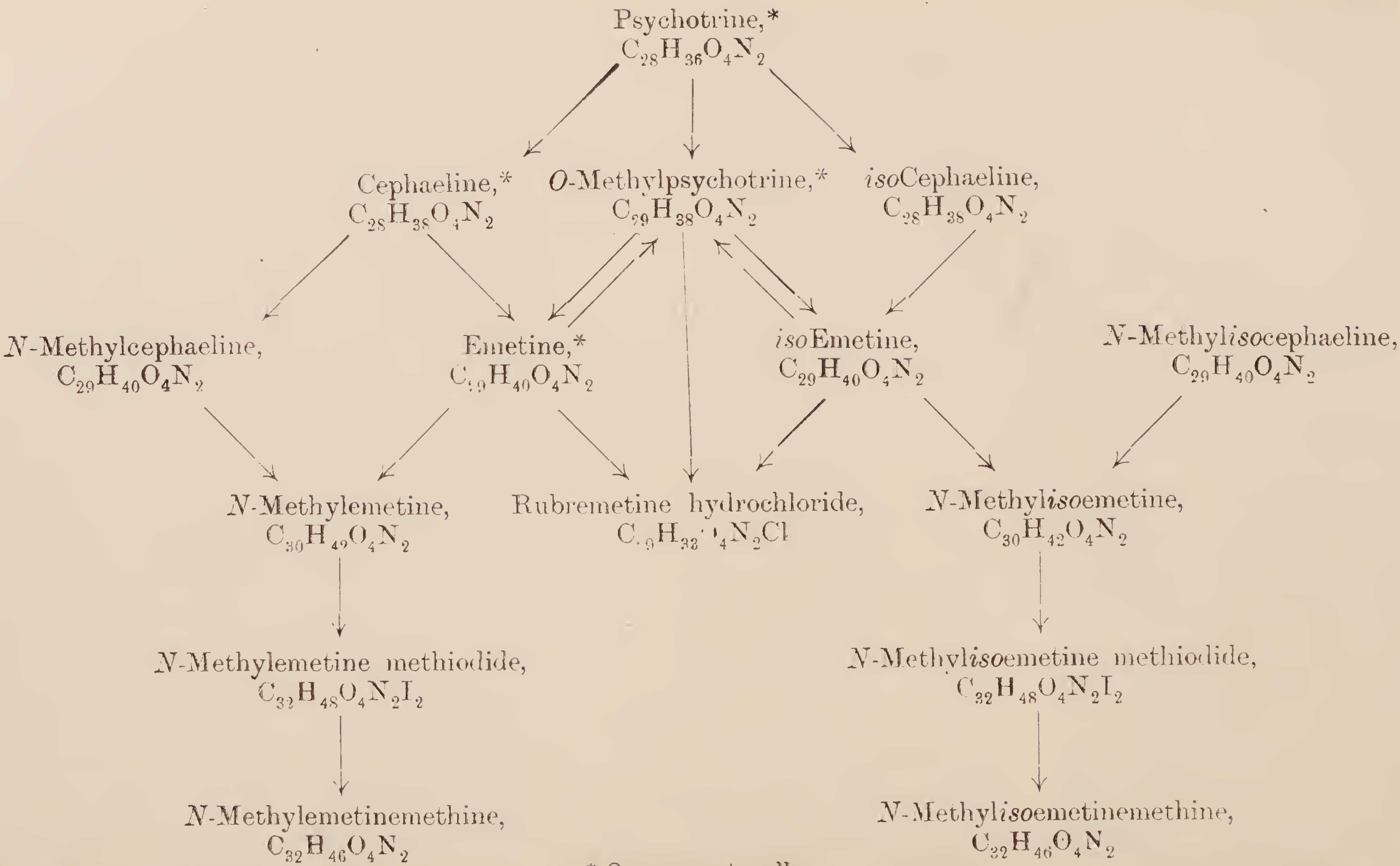
With both compounds, death resulted from acute heart failure. It was also found that *iso*emetine was practically non-emetic for cats.

A clinical trial of *iso*emetine has been carried out by Dr. G. C. Low, to whom the author's thanks are due. Whilst emetine given in amœbic dysentery nauseates the patient, but brings about the elimination of the amœbæ, Dr. Low finds that *iso*emetine is well tolerated in comparatively large doses, but does not appear to have any effect on the amœbæ.

EXPERIMENTAL.

Isolation of iso*Emetine.*

*iso*Emetine occurs together with emetine and base "C" amongst the reduction products of methylpsychotrine. In order to isolate it, the syrupy base recovered from the mother liquors of emetine hydrobromide (T., 1917, **111**, 439, line 10) is dissolved in alcohol (2 parts) and mixed with a solution of hydrated oxalic acid (0·5 part) in alcohol (5 parts), and kept for several days, when a spongy, crystalline mass slowly separates. This is collected and washed with alcohol, when crude *iso*emetine hydrogen oxalate remains. Further quantities remain in the mother liquors from the crystallisation of the hydrogen oxalate of base "C" (*ibid.*, p. 438). The crude hydrogen oxalate is dissolved in water, and the base regenerated into ether by sodium hydroxide; after removing the solvent, the residue is dissolved in a slight excess of dilute hydrobromic acid, digested with animal charcoal, and filtered, when *iso*emetine hydrobromide separates on inoculating and cooling, and is purified readily by recrystallisation from water.


Psychotrine,* $C_{28}H_{36}O_4N_2$
Cephaeline,* $C_{28}H_{38}O_4N_2$
O-Methylpsychotrine,* $C_{29}H_{38}O_4N_2$
*iso*Cephaeline, $C_{28}H_{38}O_4N_2$
N-Methylcephaeline, $C_{29}H_{40}O_4N_2$
Emetine,* $C_{29}H_{40}O_4N_2$
*iso*Emetine, $C_{29}H_{40}O_4N_2$
N-Methyl*iso*cephaeline, $C_{29}H_{40}O_4N_2$
N-Methylemetine, $C_{30}H_{42}O_4N_2$
Rubremetine hydrochloride, $C_{29}H_{33}O_4N_2Cl$
N-Methyl*iso*emetine, $C_{30}H_{42}O_4N_2$
N-Methylemetine methiodide, $C_{32}H_{48}O_4N_2I_2$
N-Methyl*iso*emetine methiodide, $C_{32}H_{48}O_4N_2I_2$
N-Methylemetinemethine, $C_{32}H_{46}O_4N_2$
N-Methyl*iso*emetinemethine, $C_{32}H_{46}O_4N_2$

* Occurs naturally.

iso*Emetine*, $C_{29}H_{40}O_4N_2$.

The base crystallises from ether in characteristic disks (circular plates) formed of radiating needles, containing $1H_2O$, which is not completely lost in a vacuum. The air-dried base softens at 92° and melts at 97—98° (corr.); the same form and melting point were observed after recrystallisation of the base from ethyl acetate.

Found, in air-dried base (from ether): C = 69·7; H = 8·5; loss in a vacuum = 2·5.

$C_{29}H_{40}O_4N_2,H_2O$ (498·5) requires C = 69·9; H = 8·5; loss of $1H_2O$ = 3·6 per cent.

The base is insoluble in water, but easily soluble in the usual organic solvents with the exception of light petroleum. Its colour-reactions with Fröhde's reagent (green) and sodium diazobenzene-*p*-sulphonate (red in the presence of sodium carbonate, little changed on the addition of dilute hydrochloric acid) are identical with those given by emetine.

The specific rotatory power of the base, dried in a vacuum, was determined in chloroform solution:

$\alpha_D - 3·33°$; $c = 3·514$; $l = 2$-dcm.; $[\alpha]_D - 47·4°$.

The *hydrochloride* was obtained as a mass of small needles by neutralising the base with aqueous hydrochloric acid, evaporating the solution to dryness, and boiling the residue with absolute alcohol. It melts and decomposes at 310° (corr.), and is easily soluble in water, but almost insoluble in absolute alcohol.

This salt is almost anhydrous, losing only 0·5 per cent. at 100°.

Found in dried salt: C = 62·6; H = 7·7; Cl = 12·8.

$C_{29}H_{40}O_4N_2,2HCl$ (553·4) requires C = 62·9; H = 7·7; Cl = 12·8 per cent.

The specific rotatory power of this salt was determined in aqueous solution, and found to be negative at high, but positive at low concentrations:

$\alpha_D - 4·70°$; $c = 15·07$; $l = 2$-dcm.; $[\alpha]_D - 15·6°$.
$\alpha_D - 0·87°$; $c = 8·134$; $l = 2$-dcm.; $[\alpha]_D - 5·3°$.
$\alpha_D + 0·38°$; $c = 4·092$; $l = 2$-dcm.; $[\alpha]_D + 4·6°$.
$\alpha_D + 0·35°$; $c = 2·259$; $l = 2$-dcm.; $[\alpha]_D + 7·7°$.
$\alpha_D + 0·23°$; $c = 0·909$; $l = 2$-dcm.; $[\alpha]_D + 12·7°$.

The *hydrobromide* crystallises from water in well-formed prisms, which contain $4H_2O$. It is easily soluble in hot, but sparingly so (1—2 per cent.) in cold water. After drying in a vacuum, it softens from 215° and gradually becomes transparent without flowing, up to 220° (corr.).

Found, in air-dried salt: C=48·8; H=7·2; loss in a vacuum, 10·1, 10·0, 10·0.

$C_{29}H_{40}O_4N_2,2HBr,4H_2O$ (714·4) requires C=48·7; H=7·1; H_2O=10·1 per cent.

Found, in dried salt: C=54·0, 54·4; H=6·7, 6·8; Br=24·7.

$C_{29}H_{40}O_4N_2,2HBr$ (642·3) requires C=54·2; H=6·6; Br=24·9 per cent.

The specific rotatory power of the hydrated salt was determined in aqueous solution:

α_D + 0·54°; c=4·153; l=2-dcm.; $[\alpha]_D$ + 6·5°.
α_D + 0·42°; c=1·989; l=2-dcm.; $[\alpha]_D$ + 10·5°.

The *hydrogen oxalate* crystallises from water in colourless prisms, which contain $5H_2O$, and melt at 92—95° (corr.). After drying at 100°, it has no definite melting point, but softens from about 150° and effervesces at about 165° (corr.). It is easily soluble in water or alcohol, but its solution in the latter deposits a colourless, spongy mass on keeping.

Found, in air-dried salt: loss in a vacuum=11·8.

$C_{29}H_{40}O_4N_2,2C_2H_2O_4,5H_2O$ (750·6) requires H_2O=12·0 per cent.

Found, in salt dried in a vacuum: C=59·8, 60·1; H=7·0, 6·8.

$C_{29}H_{40}O_4N_2,2C_2H_2O_4$ (660·5) requires C=60·0; H=6·7 per cent.

The specific rotatory power was determined in aqueous solution:

α_D + 0·25°; c=8·019; l=2-dcm.; $[\alpha]_D$ + 1·6°.
α_D + 0·50°; c=3·856; l=2-dcm.; $[\alpha]_D$ + 6·5°.
α_D + 0·50°; c=2·958; l=2-dcm.; $[\alpha]_D$ + 8·5°.
α_D + 0·33°; c=1·454; l=2-dcm.; $[\alpha]_D$ + 11·3°.

Methylation of iso*Cephaeline. Formation of* iso*Emetine.*

0·4 Gram of *iso*cephaeline (T., 1914, **105**, 1626) was dissolved in a solution of 0·05 gram of sodium in 35 c.c. of fusel oil boiling at 130—133°; 0·2 gram of anhydrous sodium methyl sulphate was added, and the mixture boiled for one and a-half hours under a reflux condenser. After acidifying with hydrochloric acid, the liquor was distilled with steam to remove the fusel oil, and the alkaloids were then regenerated to ether by means of sodium carbonate. The ethereal solution was extracted with dilute aqueous sodium hydroxide, which removed 0·15 gram of unchanged *iso*cephaeline, evaporated to dryness, and converted into the hydrobromide, when 0·17 gram of crude *iso*emetine hydrobromide was obtained. After recrystallisation from water, this salt formed prismatic needles, having the melting point previously recorded, either alone or mixed with *iso*emetine hydrobromide resulting from the reduction of methylpsychotrine. For further identification, the base was regenerated from the hydrobromide, when it crystallised from ether in the characteristic disks, melting at 97—98° (corr.), both alone and when mixed with a specimen of the base resulting from the reduction of methylpsychotrine.

Methylation of iso*Emetine. Formation of* N-*Methyl*iso*emetine and Isolation of Benzoyl*iso*emetine.*

*iso*Emetine was methylated by methyl sulphate and sodium methoxide, the resulting mixture of *N*-methyl*iso*emetine and unchanged *iso*emetine being separated by removing the latter as the benzoyl derivative, the hydrochloride of which can be extracted from aqueous solution by chloroform. The method is precisely similar to that employed for the methylation of emetine (T., 1914, **105**, 1617), to which reference may be made for further details.

*iso*Emetine, regenerated from 7·2 grams of the hydrated hydrobromide, was dissolved in a solution of 0·5 gram of sodium in 25 c.c. of methyl alcohol and treated with 2·5 grams of methyl sulphate, when 1·3 grams of *N*-methyl*iso*emetine and 2·1 grams of benzoyl*iso*emetine were obtained.

N-*Methyl*iso*emetine* crystallises from ether in clear, colourless, square tablets with bevelled edges. It melts at 152—153° (corr.), and crystallises again on cooling. It suffers no loss in a vacuum.

Found: C = 72·8; H = 8·5.

$C_{30}H_{42}O_4N_2$ (494·5) requires C = 72·9; H = 8·6 per cent.

The specific rotatory power was determined in chloroform solution:

$$\alpha_D - 2·55°;\ c = 2·550;\ l = 2\text{-dcm.};\ [\alpha]_D - 50·0°.$$

Benzoyl*iso*emetine proved to be identical with the substance previously described under this name (T., 1917, **111**, 439). It formed colourless prismatic needles from acetone, which melted at 207—208° (corr.) alone or when mixed with the preparation to which reference has been made. The specific rotatory power in chloroform solution was found to be $[\alpha]_D + 47·3°$ ($c = 2·833$).

Methylation of N-*Methyl*iso*cephaeline. Formation of* N-*Methyl*iso*emetine.*

The isomeride (T., 1914, **107**, 1624) of *N*-methylcephaeline yields *N*-methyl*iso*emetine on methylation, and is therefore *N*-methyl*iso*cephaeline.

Two grams of the pure isomeride, melting at 196—197° (corr.), were dissolved in a solution of 0·5 gram of sodium in 50 c.c. of fusel oil, boiling at 130—133°, and boiled for two hours under a reflux condenser with 1·25 grams of anhydrous sodium methyl sulphate. On working up the product in the usual way (compare, for instance, T., 1914, **107**, 1623), 1·4 grams of the phenolic base were recovered, and 0·23 gram of *N*-methyl*iso*emetine was obtained. This base melted at 152—153° (corr.) alone or when mixed with the methylation product of *iso*emetine; the specific rotatory power in chloroform solution was found to be $[\alpha]_D$ $-47·6°$ ($c=1·125$).

N-*Methyl*iso*emetine Methiodide*.

Twenty-five grams of *iso*emetine hydrobromide were dissolved in 625 c.c. of hot water, cooled, mixed with 50 c.c. of methyl iodide and 25 grams of anhydrous sodium carbonate, and heated on the water-bath. After one and three-quarter hours, the insoluble matter, which was viscous and amorphous at first, had become crystalline, and was collected. It amounted to 21·3 grams, and formed colourless, well-defined, oblong prisms which melted at 290—292° (corr.) after drying at 100°. This salt is very sparingly soluble in cold water.

Found, in air-dried salt, loss in a vacuum $=2·4$; in dried salt, $I=32·4$.

$C_{32}H_{48}O_4N_2I_2,H_2O$ (796·4) requires $H_2O=2·3$ per cent.

$C_{32}O_{48}O_4N_2I_2$ (778·4) requires $I=32·6$ per cent.

The specific rotatory power of the hydrated salt was determined in aqueous solution:

$$\alpha_D +0·6°;\ c=0·324;\ l=2\text{-dcm.};\ [\alpha]_D +92·6°.$$

The mother liquors from the crystalline methiodide were concentrated, and deposited 6·5 grams of pale orange-brown resin, which became quite hard, but was not obtained in a crystalline form. The crystalline and amorphous salts were found to give the methine in approximately equal yield.

N-*Methyl*iso*emetinemethine*, $C_{32}H_{46}O_4N_2$.

29·2 Grams of *iso*emetine hydrobromide were converted into methyl*iso*emetine methiodide by the method described above, and the combined crystalline and amorphous methiodides were converted into the anhydro-base by the method employed for methylemetinemethine (T., 1917, **111**, 445). The crude methine was neutralised with 20 per cent. aqueous oxalic acid, and gave 21·1 grams of neutral oxalate in several crops, that is, 75·4 per cent. of the theoretical yield.

*Methyl*iso*emetinemethine oxalate* crystallises from water in colourless prisms of an elongated diamond shape which are very easily soluble in water. The air-dried salt contains $4H_2O$ and melts at 122—127° (corr.); after drying at 100°, the salt melts at 133—134° (corr.).

Found, in air-dried salt: $H_2O = 10·8$, 10·7.

$C_{32}H_{46}O_4N_2,C_2H_2O_4,4H_2O$ (684·6) requires $H_2O = 10·5$ per cent.

Found, in air-dried salt: $C = 66·4$, 66·4, 66·5, 66·5; $H = 7·9$, 7·9, 7·9, 7·9.

$C_{32}H_{46}O_4N_2,C_2H_2O_4$ (612·6) requires $C = 66·6$; $H = 7·9$ per cent.

The specific rotatory power of this salt was determined in aqueous solution:

$$\alpha_D + 0·35°;\ c = 4·153;\ l = 2\text{-dcm.};\ [\alpha]_D + 4·2°.$$

*Methyl*iso*emetinemethine methiodide* separates as a crystalline powder when a concentrated ethereal solution of the methine, prepared by regeneration from the pure oxalate, is warmed with methyl iodide. The salt, so prepared, began to sinter at 155° and effervesced at 163° (corr.); when moistened with cold water, it first became gummy and then crystallised; it appeared to contain methyl iodide of crystallisation, for when it was added to boiling water effervescence took place, and an odour of methyl iodide was observed. The hot aqueous solution deposited the salt on cooling in silky needles, which melt at 178° (corr.) after drying at 100°, and effervesce at about 180°.

Found, in air-dried salt: loss at $110° = 4·0$.

$C_{34}H_{52}O_4N_2I_2,2H_2O$ (842·4) requires $H_2O = 4·3$ per cent.

Found, in dried salt: $I = 31·6$.

$C_{34}H_{52}O_4N_2I_2$ (806·4) requires $I = 31·5$ per cent.

Oxidation of iso*Emetine. Formation of Methylpsychotrine and Rubremetine.*

(1) *With One Molecular Proportion of Iodine.*—This oxidation was carried out essentially in the same way as that of emetine (T., 1917, **111**, 434), but the isolation of methylpsychotrine as hydrogen oxalate was complicated by the fact that *iso*emetine hydrogen oxalate also crystallises from moist alcohol, whereas emetine hydrogen oxalate does not.

Twenty grams of *iso*emetine hydrobromide were recrystallised from 50 c.c. of water, when 19 grams separated. After removing this, the mother liquor gave further small crops of the same salt on concentration, and eventually a liquor which no longer deposited crystals. This was shaken with aqueous sodium hydroxide and ether, and the regenerated base, amounting to 0·04 gram, was converted into the hydrogen oxalate in alcoholic solution, when 0·02 gram of colourless, somewhat spongy crystals was obtained, which, after drying at 100°, sintered at 145°, and gradually melted up to about 200°. The melting point indicates that this hydrogen oxalate did not consist wholly of methylpsychotrine hydrogen oxalate, whence the original hydrobromide contained less than 1 per cent. of methylpsychotrine.

Nine grams (part of the 19 grams) of purified *iso*emetine hydrobromide were then converted into the base and oxidised with 3·2 grams of iodine in 80 c.c. of absolute alcohol by heating for three and a-half hours at 100°.

The product was mixed with dilute sulphurous acid, evaporated to about half its volume, mixed with aqueous sodium hydroxide, and extracted with chloroform. The chloroform extract was completely extracted with dilute hydrochloric acid, dried, and distilled, when it left 2·3 grams of dark brown resin. This was extracted with small quantities of boiling water, and the filtered extracts were mixed with a small quantity of aqueous potassium iodide, when 0·9 gram of rubremetine hydriodide separated in minute red needles, which, after drying at 100°, began to melt at 177° (corr.) either alone or when mixed with rubremetine hydriodide prepared by the oxidation of emetine. The identification of the salt with rubremetine hydriodide was further confirmed by analysis. (Found, in air-dried salt, $H_2O = 13·5$; in dried salt, $I = 21·3$. Calc.: $H_2O = 13·0$; $I = 21·2$ per cent.)

The hydrochloric acid extract of the chloroform extract was mixed with aqueous sodium hydroxide and extracted with chloroform. The chloroform residue was converted into the hydrobromide, when 5·0 grams of *iso*emetine hydrobromide were recovered. The mother liquors, shaken with aqueous sodium hydroxide and ether, gave 0·7 gram of base, which was dissolved in alcohol containing 0·4 gram of hydrated oxalic acid. On inoculating with methylpsychotrine hydrogen oxalate, 0·13 gram of nearly colourless crystals, melting at 140—145° (corr.), separated. For purification, the base was regenerated from this material and again converted into hydrogen oxalate, when 0·08 gram was obtained, which melted at 145—150° (corr.), methylpsychotrine hydrogen oxalate melting at 150—155° (corr.) in the same bath, and a mixture of the two substances intermediately. The aqueous solution of the salt showed the blue fluorescence characteristic of methylpsychotrine salts. A determination of the specific rotatory power gave a low value, $[\alpha]_D + 33°$ ($c = 1$), and consequently further evidence of the identity of the substance was required. Accordingly, the base was regenerated, neutralised with dilute sulphuric acid, and the solution evaporated to dryness, then moistened with absolute alcohol and evaporated to dryness several times. Finally, it was dissolved in a few drops of absolute alcohol and inoculated with methylpsychotrine sulphate monohydrate, when a colourless, crystalline powder separated, which melted at 245° (corr.), methylpsychotrine sulphate melting at 248° (corr.), and a mixture of the two substances at 246° in the same bath.

(2) *With Ferric Chloride.*—Two grams of *iso*emetine hydrochloride were oxidised with an aqueous solution of 40 grams of commercial hydrated ferric chloride, the details of manipulation being the same as previously described for the oxidation of emetine with ferric chloride (T., 1914, **105**, 1627). After crystallisation from water, 0·45 gram of crude rubremetine hydrochloride was obtained. This was purified in the manner previously described, and identified by comparison with a specimen prepared from emetine.

Action of Sodium Amyloxide on iso*Emetine.*

The base liberated from 3 grams of *iso*emetine hydrobromide was dissolved in a solution of 1·0 gram of sodium in 50 c.c. of fusel oil (b. p. 130—133°), and boiled for fourteen hours under a reflux condenser. After the addition of 6 c.c. of hydrochloric acid and 20 c.c. of water, the fusel oil was removed by steam distillation, and the non-phenolic and phenolic bases were recovered and separated in the usual way. The latter—amounting to 0·3 gram of yellow resin—were neglected, whilst the non-phenolic bases were found to consist almost entirely of *iso*emetine, for when treated with hydrobromic acid they gave 2·3 grams of pure *iso*emetine hydrobromide, the mother liquors containing only a trace of material.

Emetine, when treated in a similar manner, was also mainly recovered unchanged, except in so far as it had become hydrolysed, and no evidence of the formation of *iso*emetine could be obtained.

Preparation and Separation of α- and β-N-Methylemetine Methiodides.

Ten grams of emetine hydrobromide were dissolved in 250 c.c. of hot water, and the solution, after cooling to some extent, was mixed with 20 c.c. of methyl iodide and 10 grams of anhydrous sodium carbonate. It was then heated on the water-bath under a reflux condenser so that the methyl iodide boiled. After three hours crystals began to form, and gradually increased in quantity; after boiling for a fourth hour, the excess of methyl iodide was removed by distillation and the liquor filtered from the first crop of crystals—8·0 grams; m. p. 210—220°; $[\alpha]_D$ −6°. On cooling, the mother liquor deposited a second crop of crystals—2·6 grams; m. p. 220—260°; $[\alpha]_D$ +32·4°—whilst a third fraction was obtained by extraction with chloroform as a nearly colourless resin (0·7 gram) which deposited crystals after solution in water. After recrystallising the first crop from water twice, the previously known α-methiodide was obtained in a pure state; it had the melting point previously recorded, namely, 225—226° (corr.), and formed prisms containing between 3 and $4H_2O$. (Found: $H_2O = 7·9$. Calc. for $3H_2O$, 6·3; for $4H_2O$, 8·5 per cent.) The specific rotatory power was determined in aqueous solution:

$$\alpha_D\ -0·23°;\ c=1·145;\ l=2\text{-dcm.};\ [\alpha]_D\ -10·0°.$$

After prolonged fractional crystallisation, there were obtained 5·35 grams of this salt in a pure state, 2·6 grams less pure, melting at 210—220°, various small crops melting between 220° and 260°, and 0·45 gram of the pure β-*methiodide*.

α-N-*Methylemetine methochloride* was prepared from the α-methiodide by double decomposition with silver chloride, concentration of the filtered solution to a syrup, and precipitation with acetone, when it formed small, colourless needles which melted at 133° (corr.) after drying at 100°, and at 200° (corr.) after drying at 110°.

Found, in air-dried salt: loss at 100—110° = 15·2.

$C_{32}H_{48}O_4N_2Cl_2,6H_2O$ (703·6) requires $H_2O = 15·3$ per cent.

Found, in salt dried at 100—110°: C = 64·2, 64·2; H = 8·1, 8·0.

$C_{32}H_{48}O_4N_2Cl_2$ (595·5) requires C = 64·5; H = 8·1 per cent.

The specific rotatory power of this salt was determined in aqueous solution:

$$\alpha_D\ -0·18;\ c=3·986;\ l=2\text{-dcm.};\ [\alpha]_D\ -2·3°.$$
$$\alpha_D\ -0·18;\ c=1·993;\ l=2\text{-dcm.};\ [\alpha]_D\ -4·5°.$$

β-N-*Methylemetine methiodide* forms long, flat plates from water, which melt at 262° (corr.) after drying at 100°. Like the α-salt, it is easily soluble in hot, but very sparingly so in cold water.

Found, in air-dried salt: $H_2O = 5·2$.

$C_{32}H_{48}O_4N_2I_2,2\frac{1}{2}H_2O$ (823·4) requires $H_2O = 5·5$ per cent.

Found, in salt dried in a vacuum: C = 49·6; H = 6·3.

$C_{32}H_{48}O_4N_2I_2$ (778·4) requires C = 49·3; H = 6·2 per cent.

The specific rotatory power was determined in aqueous solution;

$$\alpha_D\ +1·15°;\ c=0·844;\ l=2\text{-dcm.};\ [\alpha]_D\ +68·1°.$$

Formation of N-*Methylemetinemethine from the β-Methiodide.*

0·5 Gram of the β-methiodide was converted into the methine by the method used for the α-methiodide (T., 1917, **111**, 445). The crude tertiary base, extracted by ether (0·27 gram), was dissolved in alcohol and neutralised with oxalic acid, when 0·12 gram of methylemetinemethine oxalate crystallised in prisms. It melted at 82—83° (corr.), a mixture with the salt prepared from the α methiodide melting at the same temperature.

For further identification, the water of crystallisation was estimated (Found: $H_2O=18·9$. Calc.: $H_2O=18·1$ per cent.), and an approximate determination of the specific rotatory power was made [Found: $[\alpha]_D$ $-19·5°$ ($c=1·2$ in water); previously found for salt from α-methiodide, $[\alpha]_D$ $-24·6$]. It was also observed that the methine from the β-methiodide gave a hydrochloride, which crystallised from absolute alcohol in plates. A similar salt had previously been obtained from the methine prepared from the α methiodide, by the following method.

N-*Methylemetinemethine Hydrochloride.*

A quantity of the base, regenerated from the pure oxalate to ether, was dissolved in dilute hydrochloric acid and evaporated to dryness. It was next dissolved in absolute alcohol and evaporated to dryness, this operation being repeated several times. It was then dissolved in a small volume of absolute alcohol, when it separated in colourless, quadrilateral plates, which melted at 236° (corr.) after drying at 100°. This salt is very easily soluble in water.

Found, in air-dried salt: loss at 105° = 2·4, 3·7.

$C_{32}H_{46}O_4N_2,2HCl,H_2O$ (613·4) requires $H_2O=2·9$ per cent.

Found, in salt dried at 105°: Cl = 11·5, 11·5.

$C_{32}H_{46}O_4N_2,2HCl$ (595·5) requires $Cl=11·9$ per cent.

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